The bond angles of 120(±4)° indicate that the ring carbon atoms are sp^2 hybridized. The angles about the methoxy groups average 116°.

A packing diagram (Fig. 4) shows the two molecules positioned in parallel planes spaced about 4·4 Å apart. Least-squares planes calculated through the strucutre indicate that the substituted oxygen atoms along with C(15) are positioned near the plane of the ring (+0·04 Å) while the remaining non-ring carbon atoms are above and below the planes at distances from 1·2 to 1·4 Å.

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The Crystal Structure of a Proposed Fusidic Acid Intermediate

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The structure of a proposed intermediate in the synthesis of the abnormal steroid fusidic acid was determined by means of X-ray analysis. The compound, $C_{23}H_{27}O_3Br$, forms triclinic crystals, space group $P\bar{1}$, with cell dimensions $a=8{\cdot}681$, $b=7{\cdot}361$, $c=16{\cdot}077$ Å, $\alpha=90{\cdot}85$, $\beta=99{\cdot}44$, $\gamma=84{\cdot}97°$; there are two molecules in the cell. The structure was refined to an R index of 6·3% for 1979 non-zero reflections measured on a diffractometer. The results of the analysis revealed that the proposed intermediate has a structure incompatible for conversion to the desired steroid.

Introduction

A proposed intermediate (I*a*) in the synthesis of the abnormal steroid fusidic acid (II) was prepared in the laboratories of Professor W. G. Dauben at the University of California at Berkeley (Fig. 1). Subsequent conversion of the intermediate was not a trivial undertaking, and conventional methods of organic structure analysis were inconclusive. Therefore, an X-ray analysis was undertaken to establish the structure of the intermediate with certainty.

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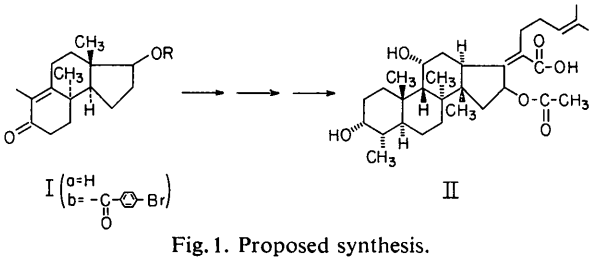


Fig. 1. Proposed synthesis.

Experimental

A suitable heavy-atom derivative (I*b*) was prepared by reacting the intermediate with 4-bromobenzoyl chloride in pyridine. The resulting reaction product was washed with sodium bicarbonate and was purified by two crystallizations from ethanol. Thin-layer chromatography (silica gel), nuclear magnetic resonance, and infrared and mass spectra revealed that the desired 4-bromobenzoate derivative had been formed in high purity.

Crystals suitable for an X-ray analysis were grown from acetone by slow evaporation. The plate-like crystals were cut to a size of 0·2×0·2×0·1 mm. A precession camera survey of the crystal indicated that it belonged to a triclinic space group, $P1$ or $P\bar{1}$. Sodium-chloride calibrated, zero level, precession photographs established approximate cell dimensions. More accurate cell dimensions were obtained with a General Electric-Datex diffractometer. Unit-cell dimensions measured on the diffractometer with nickel-filtered copper radiation were as follows:

$a=$ 8·681 ± 0·002 Å	$\alpha=90{\cdot}85\pm0{\cdot}04°$
$b=$ 7·361 ± 0·002	$\beta=99{\cdot}44\pm0{\cdot}05$
$c=16{\cdot}077\pm0{\cdot}003$	$\gamma=84{\cdot}97\pm0{\cdot}02$

Table 1. *Observed and calculated structure factors*

Within each group are values of l, $10F_o$, $10F_c$. Reflections marked* were assigned zero weight in the final least-squares cycles.

Intensity data to a resolution of 1 Å (max. sin $\theta/\lambda = 0{\cdot}5$) were collected on the General Electric–Datex diffractometer with nickel-filtered copper radiation and a scintillation counter. A θ–2θ scan technique was employed, background was counted for 10 seconds at each end of the scan, and the scan rate was 2°. min^{-1} in 2θ. A single check reflection (210) was monitored every 30 reflections and revealed no radiation damage, since

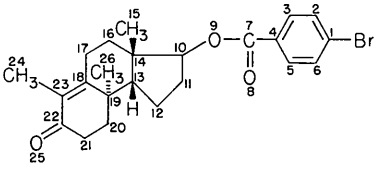
Table 2. *The* C, O, Br *parameters and their standard deviations*

Values for the bromine atom have been multiplied by 10^5, and for other atoms by 10^4. The temperature factor is in the form

$$T = \exp\{-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)\}.$$

	x	y	z	B or b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	2448 (6)	5192 (8)	2700 (3)	93 (11)	240 (17)	25 (3)	17 (22)	29 (9)	−4 (11)
C(2)	2647 (7)	4637 (7)	3543 (4)	169 (12)	156 (15)	34 (3)	−8 (22)	36 (10)	−15 (11)
C(3)	2867 (7)	5951 (8)	4158 (3)	172 (12)	169 (16)	24 (3)	9 (22)	32 (9)	19 (11)
C(4)	2907 (6)	7776 (7)	3951 (3)	93 (10)	176 (15)	21 (3)	5 (20)	24 (8)	−4 (10)
C(5)	2706 (6)	8257 (7)	3110 (3)	117 (11)	175 (15)	28 (3)	−26 (20)	33 (9)	16 (11)
C(6)	2536 (6)	6969 (8)	2474 (3)	106 (11)	190 (15)	23 (3)	7 (21)	28 (9)	24 (11)
C(7)	3050 (6)	9235 (8)	4598 (3)	102 (11)	181 (16)	22 (3)	15 (21)	25 (9)	29 (12)
O(8)	3442 (4)	10737 (5)	4486 (2)	173 (8)	159 (10)	35 (2)	−44 (15)	46 (6)	29 (7)
O(9)	2665 (4)	8685 (5)	5317 (2)	165 (8)	164 (10)	24 (2)	−55 (13)	54 (6)	−9 (7)
C(10)	2763 (6)	9894 (7)	6035 (3)	126 (11)	136 (14)	28 (3)	27 (20)	24 (9)	−3 (10)
C(11)	1617 (7)	11633 (8)	5896 (3)	167 (13)	280 (18)	38 (3)	−79 (24)	51 (10)	−20 (12)
C(12)	1640 (7)	12259 (8)	6825 (3)	190 (13)	254 (18)	32 (3)	49 (24)	34 (10)	23 (12)
C(13)	1720 (6)	10489 (7)	7335 (3)	122 (10)	169 (14)	24 (3)	37 (20)	29 (9)	21 (10)
C(14)	2283 (6)	8913 (7)	6770 (3)	120 (11)	118 (14)	26 (3)	−5 (20)	36 (9)	4 (10)
C(15)	919 (7)	7780 (7)	6456 (4)	188 (14)	186 (16)	49 (4)	−86 (24)	50 (11)	13 (12)
C(16)	3643 (7)	7693 (7)	7240 (3)	161 (12)	186 (15)	33 (3)	104 (22)	39 (10)	−3 (11)
C(17)	3361 (7)	7156 (8)	8120 (3)	187 (13)	205 (17)	27 (3)	140 (23)	20 (10)	22 (12)
C(18)	2765 (6)	8700 (7)	8640 (3)	114 (10)	149 (14)	23 (3)	−21 (20)	8 (9)	−1 (11)
C(19)	2575 (6)	10591 (7)	8255 (3)	119 (11)	139 (14)	22 (3)	−29 (20)	20 (9)	−6 (10)
C(20)	1532 (7)	11876 (7)	8722 (3)	206 (13)	149 (15)	25 (3)	7 (22)	46 (10)	7 (10)
C(21)	2045 (7)	11808 (8)	9682 (4)	195 (13)	227 (17)	40 (3)	−118 (24)	34 (10)	1 (12)
C(22)	2084 (6)	9850 (8)	9983 (3)	122 (11)	191 (16)	25 (3)	−32 (21)	4 (10)	29 (12)
C(23)	2503 (6)	8373 (7)	9417 (3)	141 (11)	136 (15)	27 (3)	−38 (20)	12 (9)	−0 (11)
C(24)	2630 (8)	6517 (8)	9780 (4)	256 (15)	183 (17)	40 (3)	−56 (25)	12 (11)	56 (12)
O(25)	1855 (5)	9568 (5)	10698 (2)	227 (9)	242 (11)	27 (2)	−19 (16)	50 (7)	16 (8)
C(26)	4213 (7)	11311 (8)	8325 (4)	150 (12)	219 (17)	50 (4)	−132 (23)	20 (10)	−38 (12)
Br(27)	20273 (8)	33802 (10)	18555 (4)	1939 (15)	2531 (21)	325 (4)	−331 (26)	307 (11)	−397 (12)

Table 3. *Bond distances*



Estimated standard deviations are slightly less than 0·01 Å.

Br(27)	C(1)	1·90 Å	C(16)	C(17)	1·54 Å	C(12)	H(32)	0·88 Å
C(1)	C(2)	1·40	C(17)	C(18)	1·51	C(13)	H(33)	0·84
C(1)	C(6)	1·37	C(18)	C(19)	1·52	C(15)	H(34)	0·95
C(2)	C(3)	1·38	C(18)	C(23)	1·34	C(15)	H(35)	0·96
C(3)	C(4)	1·39	C(19)	C(20)	1·53	C(15)	H(36)	0·86
C(4)	C(5)	1·39	C(19)	C(26)	1·55	C(16)	H(37)	1·10
C(4)	C(7)	1·48	C(20)	C(21)	1·53	C(16)	H(38)	0·90
C(5)	C(6)	1·39	C(21)	C(22)	1·52	C(17)	H(39)	1·09
C(7)	O(8)	1·21	C(22)	C(23)	1·47	C(17)	H(40)	0·90
C(7)	O(9)	1·33	C(22)	O(25)	1·22	C(20)	H(44)	1·00
O(9)	C(10)	1·44	C(23)	C(24)	1·48	C(20)	H(45)	0·90
C(10)	C(11)	1·55	C(2)	H(53)	1·08	C(21)	H(46)	0·67
C(10)	C(14)	1·53	C(3)	H(54)	1·17	C(21)	H(47)	0·90
C(11)	C(12)	1·55	C(5)	H(51)	0·96	C(24)	H(48)	0·90
C(12)	C(13)	1·54	C(6)	H(52)	1·15	C(24)	H(49)	1·13
C(13)	C(14)	1·56	C(10)	H(28)	1·04	C(24)	H(50)	0·87
C(13)	C(19)	1·55	C(11)	H(29)	0·84	C(26)	H(41)	0·95
C(14)	C(15)	1·52	C(11)	H(30)	0·69	C(26)	H(42)	1·18
C(14)	C(16)	1·52	C(12)	H(31)	0·77	C(26)	H(43)	0·96

the variation in its intensity was well within counting statistics.

The diffractometer output was processed using subprograms of the CRYRM crystallographic computer system (Duchamp, 1964). The processing included corrections for background and for Lorentz and polarization effects. It also included calculation of the F^2 value and its standard deviation for each of the 2108 reflections (129 reflections had zero intensity). The standard deviations were assigned on the basis of the following equation:

$$\sigma^2(I)=S+(B_1+B_2)\alpha^2+(dS)^2$$

where S is the scan count, B_1 and B_2 are the background counts, d is an empirical constant set at 0·02, and $\alpha=n/2mt$ where n=scan range, m=scanning speed, and t=time for background count in seconds. Finally, the data were placed on an absolute scale by Wilson (1942) statistics. No corrections for absorption were made.

The density, measured by flotation, was 1·42 g.cm^{-3}; the density calculated on the basis of 2 molecules of (I*b*) per unit cell was 1·418 g.cm^{-3}. The density data along with a Howells, Phillips & Rogers (1950) plot suggested that the crystal belonged to the space group $P\bar{1}$.

Determination and refinement of structure

The trial structure was derived by the usual Patterson and Fourier techniques in three dimensions. Full-matrix least-squares refinement of coordinates isotropic temperature factors, and scale factor reduced the R index to 12·9%. A difference Fourier synthesis indicated no misplaced or missing Br, C or O atoms. The difference Fourier synthesis was also utilized to locate the hydrogen atoms. The addition of the hydrogen atoms to the structure factor calculation and the application of anisotropic temperature factors to the C, O and Br atoms reduced the R index to its final value of 6·3%. The observed and calculated structure

Table 4. *Angles involving* C, O, Br *atoms*

Estimated standard deviations are about 0·5°.

C(2)	C(1)	Br(27)	117°	C(15)	C(14)	C(13)	109°
C(6)	C(1)	Br(27)	120	C(16)	C(14)	C(10)	112
C(2)	C(1)	C(6)	122	C(16)	C(14)	C(13)	112
C(3)	C(2)	C(1)	118	C(10)	C(14)	C(13)	104
C(4)	C(3)	C(2)	121	C(17)	C(16)	C(14)	112
C(5)	C(4)	C(7)	119	C(18)	C(17)	C(16)	115
C(5)	C(4)	C(3)	119	C(19)	C(18)	C(23)	123
C(7)	C(4)	C(3)	122	C(19)	C(18)	C(17)	117
C(6)	C(5)	C(4)	121	C(23)	C(18)	C(17)	120
C(1)	C(6)	C(5)	118	C(20)	C(19)	C(26)	110
O(8)	C(7)	O(9)	124	C(20)	C(19)	C(13)	107
O(8)	C(7)	C(4)	125	C(20)	C(19)	C(18)	110
O(9)	C(7)	C(4)	111	C(26)	C(19)	C(13)	113
C(10)	O(9)	C(7)	120	C(26)	C(19)	C(18)	109
C(11)	C(10)	C(14)	105	C(13)	C(19)	C(18)	109
C(11)	C(10)	O(9)	114	C(21)	C(20)	C(19)	113
C(14)	C(10)	O(9)	109	C(22)	C(21)	C(20)	109
C(12)	C(11)	C(10)	100	C(23)	C(22)	O(25)	122
C(13)	C(12)	C(11)	105	C(23)	C(22)	C(21)	118
C(14)	C(13)	C(19)	118	O(25)	C(22)	C(21)	119
C(14)	C(13)	C(12)	106	C(24)	C(23)	C(18)	123
C(19)	C(13)	C(12)	115	C(24)	C(23)	C(22)	115
C(15)	C(14)	C(16)	110	C(18)	C(23)	C(22)	122
C(15)	C(14)	C(10)	110				

Table 5. *Hydrogen coordinates*

Values have been multiplied by 10^4. Isotropic temperature factor for all hydrogen atoms equals 4·5.

	x	y	z		x	y	z
H(28)	3891	10300	6197	H(42)	4748	11452	9044
H(29)	733	11247	5733	H(43)	4923	10645	8008
H(30)	2246	12137	5873	H(44)	1502	13168	8518
H(31)	785	12633	6812	H(45)	542	11539	8618
H(32)	2521	12770	6986	H(46)	1269	11820	9677
H(33)	786	10351	7372	H(47)	2988	12249	9797
H(34)	1197	6646	6200	H(48)	3563	5867	9824
H(35)	630	7031	6880	H(49)	3080	6509	10480
H(36)	63	8327	6199	H(50)	1808	5893	9713
H(37)	3857	6474	6854	H(51)	2821	9518	2993
H(38)	4497	8317	7318	H(52)	2406	7516	1796
H(39)	4123	6043	8449	H(53)	2517	3191	3508
H(40)	2431	6701	7941	H(54)	2995	5565	4870
H(41)	4226	12594	8364				

factors for the refined structure are listed in Table 1.

The quantity minimized in the least-squares calculations was $\sum\omega(F_o^2-F_c^2)^2$, the weights being taken equal to $1/\sigma^2(F_o^2)$. Form factors were from *International Tables for X-ray Crystallography* (1962).

Discussion

Crystallography

The final refined atomic parameters and their standard deviations are presented in Table 2. The shifts calculated for the parameters in the final cycle of least-squares were all less than one-tenth of the standard deviation. The bond lengths and angles of the structure are given in Tables 3 and 4. The standard deviations in the coordinates, derived from the residuals and the diagonal elements of the inverse matrix of the final least-squares cycle, correspond to positional uncertainties of about 0·0007 Å for the bromine atom and about 0·005 Å for the carbon and oxygen atoms. The estimated standard deviations in the bond distances involving the Br, C, and O atoms are about 0·008 Å; and in the bond angles approximately 0·5°. Since the hydrogen positions were not refined, no error estimates

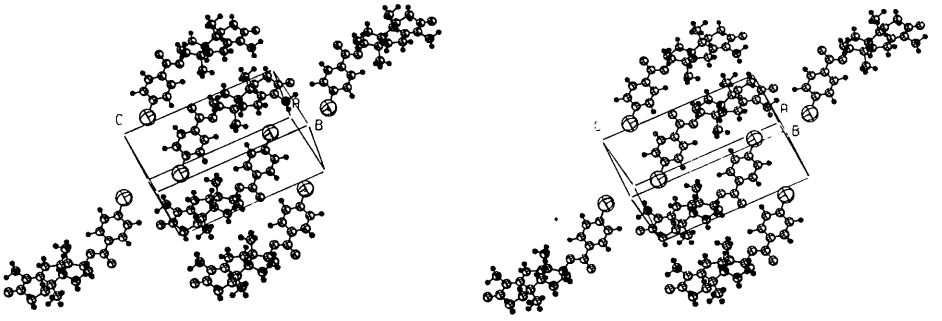


Fig. 2. Packing diagram.

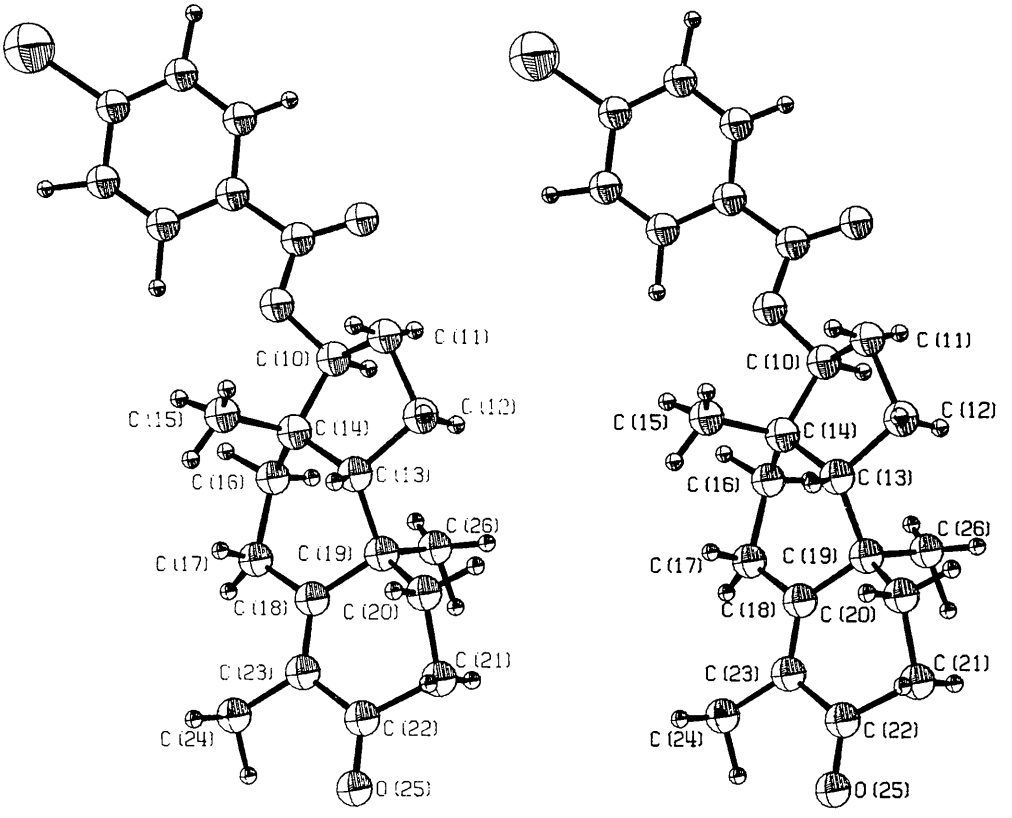


Fig. 3. Stereoscopic drawing of the structure.

have been made for distances and angles involving these atoms. The coordinates of the hydrogen atoms are listed in Table 5.

A stereoscopic view (Johnson, 1965) showing the packing of the molecules is given in Fig. 2. There are no short contacts between molecules. The shortest major-atom-to-hydrogen intermolecular distance is 2·30 Å between H(52) of the base molecule and O(25) of the molecule in translational position $(x,y,z-1\cdot0)$. The shortest hydrogen-to-hydrogen intermolecular distance is 2·38 Å between H(52) in the base molecule and H(49) of the molecule in translational position $(x,y,z-1\cdot0)$.

Chemistry

The chemical results of this analysis are illustrated in Fig. 3. It can be seen that the intermediate examined in this analysis would not be suitable for conversion to the desired steroid because of incorrect fusion of the *C–D* ring (*cis* instead of the desired *trans* fusion). The results of the X-ray analysis are in direct opposition to the result predicted by analogies present in the organic literature. The key step in preparing the *C–D* ring stereochemistry involved a stereospecific hydrogenation. Strong and relatively direct analogies in the organic literature indicated that such a hydrogen would undoubtedly result in a *trans* ring fusion. The undisputable evidence that these analogies were incorrect again amplifies the desirability of the use of X-ray analysis in organic chemistry.

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The Use of Integer Programming to Solve Crystal Structures

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This paper describes two classes of integer programming formulations of the phase problem for centrosymmetric crystals projected on to one dimension; they provide a much more complete formulation of the basic problem than do earlier integer programming approaches. One class of formulation seeks to match the structure factor expressions in terms of the phase variables with expressions in terms of atom positions; the second class matches electron-density expressions rather than structure factors. The basic advantage of this approach over more traditional methods is that it enables us to find a global minimum of the discrepancy function rather than a local minimum, obviating the need to work from many initial solutions in turn. Experience so far is limited to small artificial examples which have been solved successfully in all cases. Computational difficulties seem likely to limit the size of structure which can be solved in this way. The extension to three-dimensional structures with or without centrosymmetry is straightforward, but leads to large integer programming problems whose solution is probably beyond the scope of currently available computers and integer programming algorithms.

Integer programming problems are linear programming problems (*i.e.* the minimization of a linear function of non-negative variables subject to linear constraints) in which some of the variables are required to be integers. There are several published algorithms for the solution of such problems, though the solution of large problems is still in doubt.

The discrete nature of the phases of structure factors in centrosymmetric crystals suggests the use of integer programming in the solution of these structures. Freeman, Sime, Bennett, Dakin & Green (1963) showed that integer programming formulations could be used to express such conditions as that phases should be π or $-\pi$, electron density should be non-negative and that it should possess a specified number of peaks; Dakin (1966*a*) gives a corrected and expanded version of this approach. It appears, however, that non-negativity is not a sufficient criterion and that formulations which give adequate recognition of peaks lead to large problems which are difficult to solve. The present approach is a much more direct and complete representation of the problem. Integer variables are introduced